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Datum/Date
04-01-2005

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
90731 a/fi	00962908.0-2117/1225174

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
Sumitomo Chemical Company, Limited

COMMUNICATION OF A NOTICE OF OPPOSITION

Enclosed herewith is a copy of a notice of opposition to the European patent specified above.

An invitation to file observations and to file amendments, where appropriate, to the description, claims and drawings (Rule 57(1) EPC) will be issued separately.

The period within which such observations may be filed will not be fixed until the following conditions are met:

(a) the opposition period has expired;

(b) the notice of opposition has been examined for certain formal requirements (Rule 56 EPC).

Williams, Margit

Formalities Officer
Tel. No.: (089) 2399- 7272

Enclosure: Notice of opposition

OII Teva Tharmaceutical Industries Ltd. / fax and conf.

Printed: 03-01-2005 NEWOPPO EPO - Munich 59 00962908

20. Dez. 2004

Notice of Opposition to a European Patent

To the European Patent Office

Tabulation marks

for EPO use only

I. Patent opposed

Opp. No. OPPO (1)

Patent No. EP 1 225 174

Application No. 00962908.0

Date of mention of the grant in the European Patent Bulletin (Art. 97(4), 99(1) EPC) 17 March 2004

Title of the invention:

Anhydrous mirtazapine crystals and process for the production thereof

II. Proprietor of the Patent

Sumitomo Chemical Company Limited

first named in the patent specification

Opponent's or representative's reference (max. 15 spaces) G156210 OREF

III. Opponent

OPPO (2)

Name

Address

Teva Pharmaceutical Industries Ltd.
Patents Department
5 Basel Street
PO Box 3190
Petah Tiqva 49131

State of residence or of principal place of business: Israel

Telephone/Telex/Fax

Multiple opponents: ☐ further opponents see additional sheet

IV. Authorisation

1. Representative (Name only one representative to whom notification is to be made)

OPPO (9)

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Additional representative(s): ☒ (on additional sheet/see authorisation) OPPO (5)

2. Employee(s) of the opponent authorised for these opposition proceedings under Art. 133(3) EPC

Name(s):

Authorisation(s)

To 1./2.

☒ not considered necessary

☐ has/have been registered under No.

☐ is/are enclosed

for EPO use only

V. Opposition is filed against

— the patent as a whole [X]

— claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

— it is not new (Art. 52(1); 54 EPC) [X]

— it does not involve an inventive step (Art. 52(1): 56 EPC) [X]

— patentability is excluded on other grounds, i. e. Art. [ ]

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). [X]

(c) the subject-matter of the patent opposed extends beyond the content of the application/ of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). [ ]

VII. Facts and arguments

(Rule 55(c) EPC)
presented in support of the opposition are submitted herewith on a separate sheet (annex 1) [X]

VIII. Other requests:

Oral Proceedings, in the event that the patent is not revoked in its entirety on the basis of the written submissions.

IX. Evidence presented

for EPO use only

Enclosed = X

will be filed at a later date =

A. **Publications:** — Publication date

1 D1 Affidavit of Professor Michael B Hursthouse

Particular relevance (page, column, line, fig.):

2 D2 WO 00/62782

Particular relevance (page, column, line, fig.):

3 D2a Experimental results for Example 6 of D2

Particular relevance (page, column, line, fig.):

4 D3 Frans M. Kaspersen et al., Journal of Labelled Compounds and Radiopharmaceuticals, Vol. XXVII, No 9, 1989, pages 1055 to 1068.

Particular relevance (page, column, line, fig.):

5 D3a Experimental results for example bridging 1065 to 1066 of D3

Particular relevance (page, column, line, fig.):

6 D4 US-A-4062848

Particular relevance (page, column, line, fig.):

7 D4a Experimental results for step 4 of Example I of D4

Particular relevance (page, column, line, fig.):

Continued on additional sheet ☐

B. **Other evidence**

Continued on additional sheet ☐

for EPO use only

X. Payment of the opposition fee is made

☐ as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010)

☐

XI. List of documents

Enclosure No.		No. of copies	
0	☒ Form for notice of opposition	2 (min. 2)	
1	☒ Facts and arguments (see VII.)	2 (min. 2)	
2	Copies of documents presented as evidence (see IX.)		
2a	☒ — Publications	2 (min. 2 of each)	
2b	☐ — Other documents	(min. 2 of each)	
3	☐ Signed authorisation(s) (see IV.)		
4	☐ Voucher for payment of fees and costs (see X.)		
5	☐ Cheque		
6	☐ Additional sheet(s)	(min. 2 of each)	
7	☒ Other (please specify here): Additional Representatives Sheet	2	

XII. Signature of opponent or representative

Place London, England

Date 16 December 2004

Jo Bradley

BRADLEY, Josephine Mary

Please type name under signature. In the case of legal persons, the position which the person signing holds within the company should also be typed.

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EP 1 225 174 B (Application No. 00962908.0)

Sumitomo Chemical Co. Ltd.

Opposition by Teva Pharmaceutical Industries Limited

Facts and Arguments in Support of the Opposition

1. Facts and Arguments in accordance with Rule 55(c) EPC

The Opponent requests that the patent be revoked in its entirety under Articles 100(a) and (b) EPC. The Opponent relies on the following documents:

D1 Affidavit of Professor Michael B Hursthouse

D2 WO 00/62782

D2a Experimental results for Example 6 of D2

D3 Frans M. Kaspersen et al., Journal of Labelled Compounds and Radiopharmaceuticals, Vol. XXVII, No 9, 1989, pages 1055 to 1068.

D3a Experimental results for example bridging 1065 to 1066 of D3

D4 US-A-4062848

D4a Experimental results for step 4 of Example I of D4

2. The Patent

2.1 Claims to Anhydrous Mirtazapine Crystals - Claims 1 to 6

Claims 1 to 6 of the opposed patent relate to anhydrous mirtazapine crystals which crystals are defined in terms of a hygroscopicity.

Independent claim 1 is in the following terms:

> *Low-hygroscopic anhydrous mirtazapine crystals having a hygroscopicity of not more than 0.6 % by weight when the crystals are*

stored in air having a relative humidity of 75 % at 25 °C under atmospheric pressure for 500 hours.

Claim 2 is dependent on claim 1.

Independent claim 3 is as follows:

A process for preparing anhydrous mirtazapine crystals having a hygroscopicity of not more than 0.6 % by weight when the crystals are stored in the air having a relative humidity of 75 % at 25 °C under atmospheric pressure for 500 hours, characterised by drying crystals of a mirtazapine hydrate.

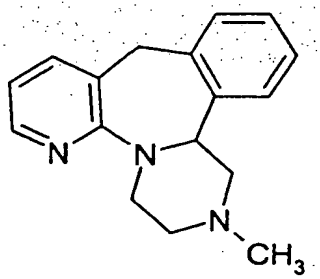
Claims 4 to 6 are process claims, each ultimately dependent on claim 3.

2.2 Claims to Crystals of Mirtzapine Hydrate – Claims 7 to 11

Claims 7 to 11 of the opposed patent relate to crystals of mirtazapine hydrate. Claim 7 related to crystals of a specific formula. Claims 8 to 11 are not so-limited.

Independent claim 7 is as follows:

A crystal of mirtazapine hydrate represented by the formula (I):



$.^{1}/n\ (H_2O)$

wherein n is an integer of 1 to 5.

Formula (I) specifies that n is an integer of 1 to 5. Claim 7 therefore specifically covers five embodiments: the monohydrate (n = 1); the hemihydrate (n = 2); and the hydrates formed when n = 3, 4 and 5.

Independent claim 8 is as follows:

> *A process for preparing crystals of a mirtazapine hydrate, characterised by crystallizing a crude mirtazapine using a water-soluble organic solvent and water.*

Claims 9 to 11 are process claims, each ultimately dependent on claim 8.

3 Technical Background to the Crystals of Mirtazapine Hydrate of Claim 7

Claim 7 covers five embodiments of crystals of mirtazapine hydrate and these are specifically crystals having a ratio of mirtazapine molecules to hydrate molecules of 1:1, 1:2, 1:3, 1:4 and 1:5. D1, which is an Affidavit of Professor Michael B Hursthouse, shows that it is physically impossible to form the monohydrate crystal, (n = 1). Therefore claim 7 covers an embodiment which does not exist.

4 Priority

The opposed patent claims priority from three applications: JP 33304999 filed on 24 November 1999; JP 2000067476 filed on the 10 March 2000; and PCT/JP00/04835 filed on 19 July 2000.

4.1 Claims 1 to 6 are not entitled to claim priority from JP 33304999 filed on 24 November 1999

Claims 1 to 6 relate to anhydrous mirtazapine crystals and processes for preparing the same. JP 33304999 contains no disclosure relating to such crystals and therefore claims 1 to 6 are not entitled to claim priority from JP 33304999.

4.2 Claim 7 is not entitled to claim priority from JP 33304999 filed on 24 November 1999

It is well established in case law that a priority document must give an enabling disclosure of the subject matter for which priority is claimed (G2/98, T206/83). Although JP 33304999 literally discloses the hydrate formula of claim 7 (formula (I)), it does not contain an enabling disclosure for this claim.

Claim 7 covers five embodiments: the monohydrate (n = 1); the hemihydrate (n = 2); and the hydrates formed when n = 3, 4 and 5.

JP 33304999 does not provide any guidance as to how to produce a mirtazapine hydrate crystal in which the ratio of mirtazapine molecules to hydrate molecules is as in all of the five ratios specified in claim 7, i.e., specifically, 1:1, 1:2, 1:3, 1:4 and 1:5. JP 33304999 provides only one example of the formation of a mirtazapine hydrate. This is Example 1 in which the hydrate has a water content of 2.3 wt % which corresponds to n = 2.88, a non-integer.

Therefore there is no implicit or explicit teaching in JP 33304999 of how a person skilled in the art would produce a mirtazapine hydrate of formula (I) which has varying values of the integer n falling within the whole interval 1 to 5 as claimed and, in particular, with endpoints 1 and 5. The subject matter of claim 7 cannot be directly and unambiguously derived from JP 33304999 as a whole. Thus, other than for when n = 2.88 (2.3 wt % water), claim 7 is not entitled to priority from JP 33304999 (T 977/98, G2/98).

Assuming that the only example provided in JP 33304999 is reproducible, we submit that this priority document only provides an enabling disclosure for a crystal of mirtazapine hydrate having a water content of 2.3 wt %.

Furthermore, it is physically impossible to form the monohydrate crystal (n = 1) as is explained in the Affidavit of Professor Michael B Hursthouse (D1). Therefore claim

7 covers an embodiment which does not exist. It is therefore not surprising that JP 33304999 does not provide an enabling disclosure for this embodiment of claim 7.

4.3 Claims 8 to 11 are not entitled to claim priority from JP 33304999 filed on 24 November 1999

Claim 8 specifies a process whereby crude mirtazapine is crystallised using a water-soluble organic solvent and water. There is no corresponding basis for the term "water-soluble organic solvent" in JP 33304999. Claim 8 and, for the same reasons, claims 9 to 11 are therefore not entitled to claim priority from JP 333049999.

Furthermore, there is no disclosure in JP 33304999 of the process step in claim 11 whereby the temperature of the solution of the mirtazapine, water-soluble organic solvent and water is adjusted to 0 °C to 30 °C.

4.4 D2 (WO 00/62782) is prior art under Art 54(3) EPC for claims 1 to 11.

D2 claims priority from two applications: US 19990130047 filed on 19 April 1999 and US20000182745 filed 16 February 2000. As the earliest priority date that can be claimed for claims 1 to 11 of the opposed patent is 10 March 2000, i.e. later than these dates, D2 is prior art under Art 54(3) EPC for all of these claims. Thus, subject matter of D2 that is disclosed in US19990130047 and US2000182745 must be considered with respect to the novelty of claims 1 to 11.

5 Insufficiency (Article 83 EPC)

The opposed patent is insufficient because it does not disclose the alleged inventions in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Specifically, although examples are provided as to how to prepare a specific hydrate (the hemihydrate) falling within the scope of claim 7, no description of how to prepare the other embodiments (n = 1, 3, 4, 5) is provided. The Opponent

considers this relevant as if it is argued that "routine variation" will yield these other hydrates, (a) this is technically impossible for at least one embodiment (n=1, see above) and, (b), this renders the claim inevitably obvious from the prior art as discussed below. The patent does not describe a pioneering invention or provide teaching capable of generalisation. A sufficient teaching is therefore required across the whole scope of the claims (see for example, T409/91 and T435/91).

5.1 Claims 1 and 2

Claim 1 relates to an anhydrous crystal of mirtazapine having a desired low hygroscopic property. Claim 1 is couched in terms of a result to be achieved and therefore covers all anhydrous crystals having the low hygroscopic property defined in the claim. However, the opposed patent provides an enabling disclosure for only one anhydrous crystal which it reports to have this property and that is the crystal formed by the process described in Example 7. The patent does not provide an enabling disclosure over the whole scope of claim 1 and thus claim 1 is insufficient. Claim 2 is dependent on claim 1 and is insufficient for the same reasons given for claim 1.

5.2 Claims 3 to 6

Claims 3 to 6 relate to a process for preparing anhydrous mirtazapine crystals that have the hygroscopic property defined in claim 1. Again, the opposed patent only provides an enabling disclosure of a process for preparing the anhydrous crystal formed in Example 7 and does not provide an enabling disclosure across the whole breadth of scope of each of claims 3 to 6. Each of claims 3 to 6 are therefore insufficient.

5.3 Claim 7

Claim 7 is insufficient because the disclosure of the opposed patent does not allow the alleged invention of claim 7 to be performed over all of the embodiments of claim 7. As discussed in section 3.2 above, claim 7 covers an embodiment that is physically impossible, mirtazapine monohydrate. As a result, the opposed patent is

fundamentally insufficient. As with the priority document, it is therefore not surprising that the opposed patent does not contain any examples or direction on how to obtain this particular embodiment. Again, we note that although the opposed patent provides several examples of how to form mirtazapine hydrates, the only hydrate formed and reported to conform to formula (I) is the hemihydrate (see Examples 6 and 8 of the opposed patent). This apparent difficulty in producing mirtazapine hydrates of formula (I) supports the objection that claim 7, throughout its scope, is insufficient. The opposed patent does not provide enough information for a person skilled in the art to form all of the mirtazapine hydrate crystals within the scope of claim 7.

This argument also applies to claim 5. Claim 5 relates to a process for preparing anhydrous mirtazapine crystals according to claim 3 wherein the crystal of the mirtazapine hydrate is represented by the formula (I). As the opposed patent does not sufficiently disclose mirtazapine hydrates throughout the full scope of formula (I), it does not sufficiently disclose the process of claim 5 throughout the whole scope of the claim.

6 Lack of Novelty (Article 54 EPC)

Claims 1 to 11 lack novelty.

6.1 Claim 1

Claim 1 lacks novelty over D2. The inevitable result of carrying out Example 6 of D2 would appear to be an anhydrous crystal according to claim 1. D2 is relevant prior art under Article 54(3) EPC as described in section 4.4 above.

Repetition of Example 6 of D2 shows that the process of said example forms mirtazapine hydrate crystals having a water content of 3.2 wt % water, i.e., n = 2 (the hemihydrate) prior to drying and that, after drying under vacuum, the mirtazapine crystals contain 0.2 wt % water (D2a). The preparation and drying of the crystals are under similar conditions to those described in the Examples 6 and 7 of the opposed

patent. It therefore would appear that anhydrous crystals formed by Example 6 of D2 will inevitably have the same hygroscopic properties as those formed by Example 7 of the opposed patent.

6.2 Claim 2

Claim 2 lacks novelty over D2. The mirtazapine crystal product of Example 6 of D2 has a water content of 0.2 wt % water, i.e. less than 0.5 % by weight as per the additional feature claimed in claim 2. Therefore claim 2 lacks novelty over D2 also.

6.3 Claim 3

Claim 3 lacks novelty over D2. Example 6 of D2 discloses a process whereby crystals of mirtazapine hemihydrate are dried to form anhydrous crystals having a water content of 0.2 wt %. As stated above, it would appear that the anhydrous mirtazapine so formed will inevitably have the hygroscopic property defined in both claims 1 and 3. Therefore D2 is novelty-destroying for Claim 3.

6.4 Claim 5

Claim 5 lacks novelty over D2. Claim 5 specifies that the mirtazapine hydrate used is of formula (I). The mirtazapine hydrate crystals initially formed in Example 6 of D2 are mirtazapine hemihydrate crystals. This is evidenced by the fact that they have a water content of 3.2 wt %. As mirtazapine hemihydrate falls within formula (I), D2 is novelty-destroying for Claim 5.

6.5 Claim 6

Claim 6 lacks novelty over D2. The mirtazapine hydrate of Example 6 of D2 is dried at 60 °C under vacuum, i.e. it is heated under reduced pressure to dry the crystals as specified in claim 6. Therefore D2 is novelty-destroying for claim 6.

6.6 Claim 7

Claim 7 lacks novelty over D2. Example 6 of D2 describes the preparation of crystals of mirtazapine hemihydrate, which crystals fall within formula (I) specified in claim 7. Thus claim 7 lacks novelty over D2.

Claim 7 lacks novelty over D3. Should the Opposition Division be of the opinion that claim 7 covers crystals of mirtazapine hydrate of formula (I) where n is a non-integer, then claim 1 will lack novelty over D3. The example bridging pages 1065 and 1066 of D3 describes the crystallisation of mirtazapine from a methanol/water solution. Repetition of this example (D3a) gives a mirtazapine hydrate crystal having a water content of 2.6 wt % (n = 2.5).

Claim 7 lacks novelty over D4. Should the Opposition Division be of the opinion that claim 7 covers crystals of mirtazapine hydrate of formula (I) where n is a non-integer, then claim 1 will also lack novelty over D4. Repetition of the step 4 of Example I of D4 (see D4a) gives a crystal of mirtazapine hydrate having a water content of 2.8 wt % (n = 2.4).

6.7 Claim 8

Claim 8 lacks novelty over D2. In Example 6 of D2, mirtazapine hemihydrate is crystallised from an ethanol and water mixture and thus is crystallised using a water-soluble organic solvent and water. D2 is therefore novelty-destroying for claim 8.

Claim 8 lacks novelty over D3. The example bridging pages 1065 and 1066 of D3 describes the crystallisation of mirtazapine from a methanol/water solution. Repetition of this example (D3a) gives a mirtazapine hydrate crystal having a water content of 2.6 wt % (n = 2.5). Claim 8 lacks novelty over this disclosure.

6.8 Claim 9

Claim 9 lacks novelty over D2. The ethanol and water mixture used in Example 6 of D2 is a mixed solvent of a water-soluble organic solvent and water. D2 is therefore novelty-destroying for claim 9.

Claim 9 lacks novelty over D3. As mirtazapine hydrate formed in the example bridging pages 1065 and 1066 of D3 is crystallised from a methanol/water solution, D3 discloses the process of claim 9.

6.9 Claim 10

Claim 10 lacks novelty over D2. In Example 6 of D2, the water is added dropwise to a solution of mirtazapine in ethanol. D2 therefore discloses the additional feature of claim 10.

Claim 10 lacks novelty over D3. Claim 10 is dependent on claim 8 and includes the additional feature that the crude mirtazapine is first dissolved in the methanol and then water is added to the resulting solution. D3 discloses the subject matter of claim 8 (see section 5.7 above) and inherently discloses the additional feature that the crude mirtazapine is first dissolved in the methanol and then water is added to the resulting solution.

6.10 Claim 11

Claim 11 lacks novelty over D2. In Example 6 of D2, the mirtazapine is dissolved in ethanol, water is added to the solution and the resultant solution is cooled to 10 °C. D2 therefore discloses the additional feature of claim 11.

Claim 11 lacks novelty over D3. Claim 11 is dependent on claim 10 and introduces the feature of adjusting the temperature of the solution containing the crude mirtazapine, the water-soluble organic solvent and the water to between 0 and 30 ° C to the process of claim 10. This feature is inherently disclosed in D3.

7 Lack of Inventive Step (Article 56 EPC)

In the alternative, claims 1 to 11 lack an inventive step.

The problem to be solved by this invention is the provision of a process capable of efficiently preparing a high-purity mirtazapine from a crude mirtazapine, and anhydrous mirtazapine crystals having low hygroscopic properties and a process for preparing the same and crystals of a mirtazapine hydrate which are useful as a preparation intermediate for the anhydrous mirtazapine crystals and a process for preparing the same (paragraph [0007] of opposed patent).

With respect to claims 1 to 6, it is the opponent's view that the skilled person, having repeated a prior art method and obtained a hygroscopic mateial e.g. containing 2.5 wt % water, would inevitably consider drying said material to obtain a stable anhydrate.

7.1 Claims 1 and 2

Claim 1 relates to an anhydrous crystal of mirtazapine having a desired low hygroscopic property. Claim 1 is couched in terms of a result to be achieved and amounts to no more than a claim to the underlying problem. There is no inventive merit associated with claiming a problem known in the art (paragraph [0006] of the opposed patent). Claim 1 therefore lacks an inventive step. The same objection applies to claim 2. Claim 2 relates to the subject matter of claim 1 and further specifies that the crystals have a water content of not more than 0.5 % by weight. There is no inventive merit in selecting this particular value of water content and certainly none has been demonstrated by the patentee. Claim 2 therefore lacks an inventive step.

Claim 1 lacks an inventive step over D3. When faced with the problem of preparing anhydrous mirtazapine crystals having low hygroscopic properties and with the teaching of D3, the person skilled in the art would simply take the hydrate crystals of D3 and subject them to drying by known methods. Thus the person skilled in the art would arrive at the anhydrous crystals of claim 1. Again, the choice of crystals

having a water content of less than 0.5 % by weight has no inventive merit. Claim 2 therefore lacks an inventive step over D3.

7.2 Claims 3, 4 and 6

Claims 3, 4 and 6 lack an inventive step over D3. D3 discloses the preparation of mirtazapine hydrate crystals. Again, when faced with the problem of preparing anhydrous mirtazapine crystals having low hygroscopic properties and with the teaching of D3, the person skilled in the art would simply take the hydrate crystals of D3 and subject them to drying by known methods. Pulverising the crystals to aid drying and drying by heating at reduced pressure are standard laboratory methods which form part of the common general knowledge of the person skilled in the art. Thus claims 3, 4 and 6 lack an inventive step over D3.

7.3 Claim 5

The patentee has not demonstrated the process of claim 5 works for all embodiments of claim 5. The opposed patent contains one example to the preparation of anhydrous mirtazapine using a hydrate of formula (I), i.e. Example 7 of the opposed patent in which mirtazapine hemihydrate is used. There are no examples to the preparation of the anhydrous crystals of mirtazapine for the other embodiments of claim 5, i.e. when n = 1, 3, 4 and 5 in formula (I). During drying it is possible that the crystal structure of the hydrate may crumble and the extent of this may differ depending on the particular hydrate. It follows that it is not credible that all of the embodiments of formula (I) will produce the desired anhydrous crystals in the method of claim 3. Based on this and the fact that at least one of the embodiments of formula (I) does not exist, claim 5 lacks an inventive step.

Claim 5 also lacks an inventive step over D3 for the same reasons as discussed in section 6.2 above. Furthermore, the patentee has not demonstrated that there is any benefit to be had in utilising the specific hydrates of formula (I) over the hydrate produced in D3.

7.4 Claim 7

Claim 7 relates to crystals of mirtazapine hydrate of formula (I), no matter how they are made. Again, the patentee has not demonstrated the preparation of crystals of mirtazapine hydrate of formula (I) across the whole scope of the formula and, as at least one of the embodiments of formula (I) is not technically feasible, claim 7 lacks an inventive step.

Again, when faced with the problem of providing crystals of mirtazapine hydrate useful as a preparation intermediate for the anhydrous crystals, the person skilled in the art would simply start by with the crystals available in the art such as those disclosed in D3. The patentee has not demonstrated that there is any particular technical advantage associated with the choice of the specific hydrates of formula (I) over those disclosed in D3. Claim 7 therefore lacks an inventive step over D3.

7.5 Claim 10

In the alternative, Claim 10 lacks an inventive step over D3. There are a limited number of variations of how mirtazapine can be crystallised from methanol and water. It would be obvious for a person skilled in the art, in attempting such a crystallisation, to first dissolve the crude mirtazapine in the methanol and then add water to the resulting solution. Thus in seeking to solve the problem of providing a process for preparing a particular hydrate crystal, the person skilled in the art would employ the process of claim 10.

7.6 Claim 11

In the alternative, claim 11 lacks an inventive step over D3. Claim 11 is dependent on claim 10 and introduces the feature of adjusting the temperature of the solution containing the crude mirtazapine, the water-soluble organic solvent and the water to between 0 and 30 ° C to the process of claim 10. The patentee has not demonstrated that there is any particular benefit to selecting this particular temperature range or that this step differs from standard laboratory crystallisation practice.

8 Opponent's Requests

In light of the above comments, the Opponent requests:

(i) that the Patent be revoked in its entirety; and

(ii) oral proceedings in the event that the Patent is not to be revoked in its entirety based on the written submissions.

For the Opponents

Teva Pharmaceutical Industries limited

BRADLEY, Josephine Mary

Authorised Representative

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European Patent Office,
Directorate General 2,
D-80331 Munich,
Germany.

Our Ref: G156210 NJN JNB CHM

CONFIRMATION

16 December 2004

Dear Sirs,

European Patent No. 1 225 174 (Application No. 00962908.0)
Sumitomo Chemical Co. Ltd.
Opposition by Teva Pharmaceutical Industries Ltd.

On behalf of:

Teva Pharmaceutical Industries Ltd.
Patents Department
5 Basel Street
PO Box 3190
Petah Tiqva 49131
Israel

we hereby give Notice of Opposition to the above-identified Patent. The Opposition Fee is being paid from our Deposit Account No. 28050042. In the event that instructions regarding payment of the fee do not reach you in time, you are hereby authorised to debit the fee from our Deposit Account.

We enclose the following documents in duplicate:

1. Notice of Opposition
2. Facts and Arguments in support of the Opposition
3. Documents D1-D4a.

We request revocation of the Patent in its entirety, and Oral Proceedings in the event that the Patent is not to be revoked on the basis of the written submissions.

Yours faithfully,
for D Young & Co

Josephine Mary Bradley

Enc.

AFFIDAVIT OF PROFESSOR MICHAEL B HURSTHOUSE CONCERNING THE OPPOSITION TO EP 1 225 174 B BY TEVA PHARMACEUTICAL INDUSTRIES LTD.

1. I, the undersigned Michael B Hursthouse, of University of Southampton, Highfield, Southampton SO17 1BJ, England, having been warned that I must state the truth and that I shall be liable to the penalties prescribed by law should I fail to do so, hereby declare in writing as follows:

2. I have been asked to investigate the possibility of the hemihydrate crystal structure described in EP 1 225 174 B ("the Patent") being able to support water content equivalent to that of a monohydrate.

3. Figures 3 to 7 of the Patent relate to crystalline mirtazapine hemihydrate. The crystallographic unit cell for crystalline mirtazapine hemihydrate contains four molecules of mirtazapine to two molecules of water. Each water molecule occupies a cavity around a centre of inversion, with each water molecule disordering over two sites, one site on each side of the centre.

4. In the Examples given in the Patent, the maximum water content in any preparation is never more than that equivalent to the hemihydrate (3.2 wt % water). The crystallisations in the examples are from solutions with large excesses of available water and this indicates that the system clearly does not wish to form a hydrate having a water content higher than that of the hemihydrate. On this basis alone, I believe that crystalline mirtazapine monohydrate would be unlikely to form.

5. To investigate this I have used a facility in a public domain program PLATON (downloadable from xraysoft.chem.uu.nl, see also reference Spek A.L., (1990) Acta Cryst. A46, C34). This is much used in the area of crystal structure assessment to explore the possibility of free space within a structure, for example, in case the presence of solvate molecules has been missed in the analysis or whether such could further be accommodated. For the mirtazapine structure as reported, I made two calculations as follows.

   (a) The first calculation used the structure as reported in EP 1 225 174 B, with all the water molecules present, i.e. with each water molecule fully occupying one of the sites around each centre of inversion. The aim of this calculation was to show whether a second molecule could occupy the associated second site and, whether any other sites existed that could accommodate a water molecule. The output indicated that it was not feasible to squeeze a second water molecule into the original cavity and that there were no further voids in the structure.

   (b) The second calculation used the structure as reported in EP 1 225 174 B, but with the water molecules omitted completely. The aim of this calculation was to obtain an effective volume of the cavity used by the water molecule. The calculation showed that the volume of the cavity

occupied by the water molecule is 52 Å^3. The program output includes approximate volumes for different kinds of solvent. For a hydrogen bonded water molecule, the value is given as ca. 40 Å^3. Therefore the cavity is just slightly larger than one water molecule. However, it is far too small to accommodate a second water molecule. The program also indicates that there are no further cavities in the crystal structure with volumes greater than 15 Å^3.

6. These calculations show quite clearly that the formation of a full hydrate is not feasible, under ambient conditions.

I HEREBY DECLARE that the signature hereunder is my signature, and that the statements in my affidavit are true.

.....

Michael B Hursthouse
December 2004

D2a

A recrystallisation of mirtazapine was carried out as described in Example 6 of WO 00/62782 (D2). The percentage water content, melting point, IR spectrum and colour of the resulting crystals immediately before and after drying were ascertained and are given in Table D2a below.

Table D2a

	Before Drying	After Drying
Water content (wt %)	3.2	0.2
Melting point (° C)	115.7	115.7
IR peaks (cm^{-1})	1586 1568 1444	1587 1566 1467 1445
Colour	white to creamy	white to creamy

D3a

Mirtazapine was prepared in accordance with the example entitled [^{13}C]-org 3770 ^{1}C which bridges pages 1065 and 1066 of Frans M. Kaspersen et al., Journal of Labelled Compounds and Radiopharmaceuticals, Vol. XXVII, No 9, 1989 (D3).

Reagents:	9.6 g	2-(4-methyl-2-phenyl-1—piperazinyl)-3-pyridine methanol (hydroxy NMPP) CN = 422302803
	20.0 ml	concentrated H_2SO_4

9.6 g of the hydroxy NMPP was added to a three necked flask equipped with a mechanical stirrer, thermometer and condenser and was cooled to – 40 °C. 20.0 ml of concentrated H_2SO_4 was added dropwise over 1 hour. The mixture was stirred for two hours at 60 °C. A clear solution was obtained. After cooling to room temperature (22-25 °C), 24.0 ml of water was added. After cooling to – 10 °C, 55 ml of NH_4OH (25 %) was added dropwise until a pH of 10 was reached. An oily product separated. This oily product was extracted using 250.0 ml of ethyl acetate. Phases were separated and the aqueous layer was separated using 2 x 100 ml of ethyl acetate. The ethyl acetate extracts were combined and dried over Na_2SO_4, filtered and evaporated to dryness to give 8.73 g crude mirtazapine-1. This was stored for several days at room temperature (22-25 °C).

4.0 g of the resultant mirtazapine was purified by column chromatography over 60.0 g Alox B (elution with hexane/ethylacetate 7:3 v/v IL). The fractions were analysed by TLC (aluminium sheets silica gel 60 F254) mobile phase hexane/ethyl acetate/methanol 7:3:1. The collected fractions were evaporated to dryness to give 3.47 g of mirtazapine-2. 100 ml of n-hexane containing 1 % methanol was added to the mirtazapine-2 and heated to reflux. The clear solution was filtered twice with 0.43 g charcoal. The mother liquid was evaporated to dryness to give 3.15 g mirtazapine-3.

The 3.15 g of mirtazapine-3 was suspended in 20.0 ml methanol:water (1:1) and heated to reflux. 17 ml of methanol:water (1:1) was added to the suspension dropwise at reflux until complete dissolution. After a clean solution was obtained, it was allowed to cool until room temperature (22-25 °C) was reached. The suspension was filtered at room temperature and washed with 10 ml methanol:water (1:1). The resultant white crystals were dried for 17 hours at 40 °C under vacuum (10-15 mmHg). 2.9 g of crystalline mirtazapine was obtained.

Table D3a contains results of analysis of the mirtazapine so-obtained.

Table D3a

Water content (wt %, Karl Fischer method)	2.6
Melting point (° C)	120.9
UV-ethanol	Max 294 nm; E=210

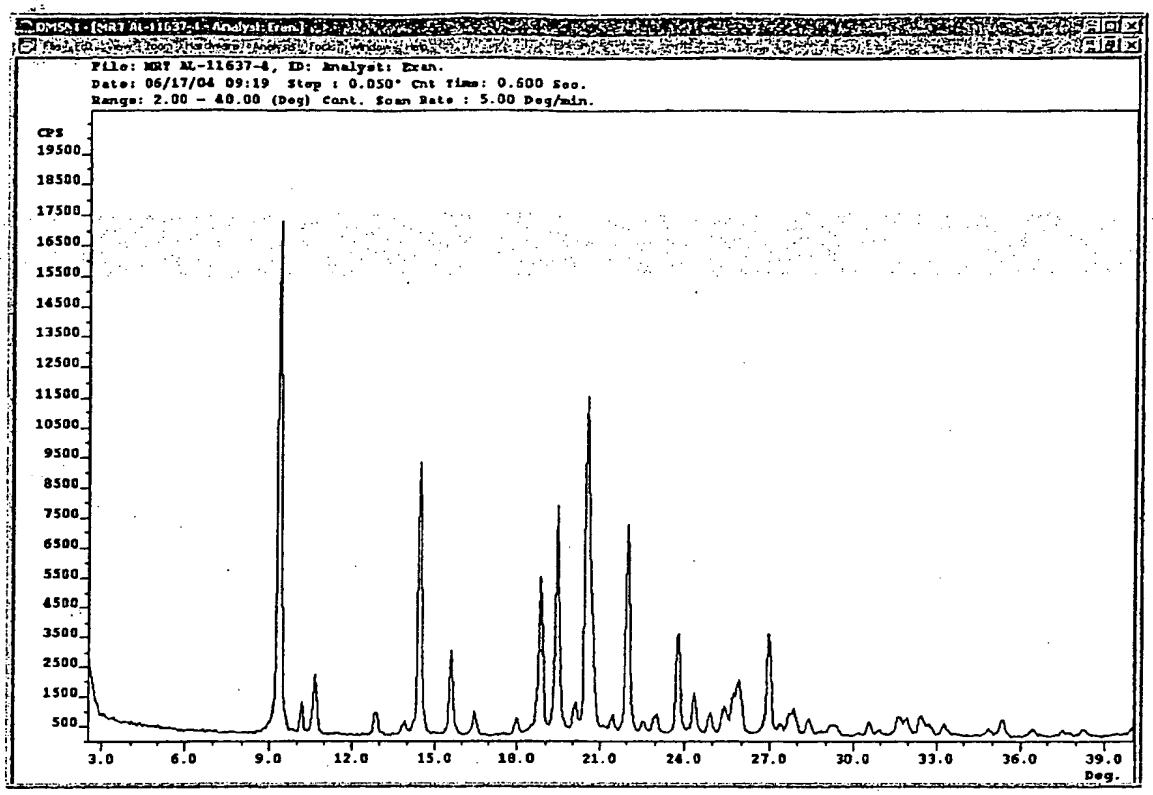
Figure 1 is an X-ray diffraction spectrum of the mirtazapine.

Details of the method:

Instrument:	Scintag X-ray powder diffractometer model X'TRA or equivalent, Cu tube, solid state detector
Sample holder:	a round standard aluminiunm sample holder with round zero background quartz or silicon plate with cavity of 25 mm (diameter) x 0.5 mm (depth)
Range:	2-40 degrees two-theta
Scan mode:	continuous scan
Step size:	0.05 deg.
Scan rate:	3 deg./min

Sample preparation: a small amount of powder was gently gound in an agate mortar with a pestle. The sample holder was filled with the powder and a somooth surface was formed by pressing with a glass plate.

Figure 2 is an IR spectrum of the mirtazapine.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Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 5.00 Deg/min.
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19500
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17500
16500
15500
14500
13500
12500
11500
10500
9500
8500
7500
6500
5500
4500
3500
2500
1500
500
3.0
6.0
9.0
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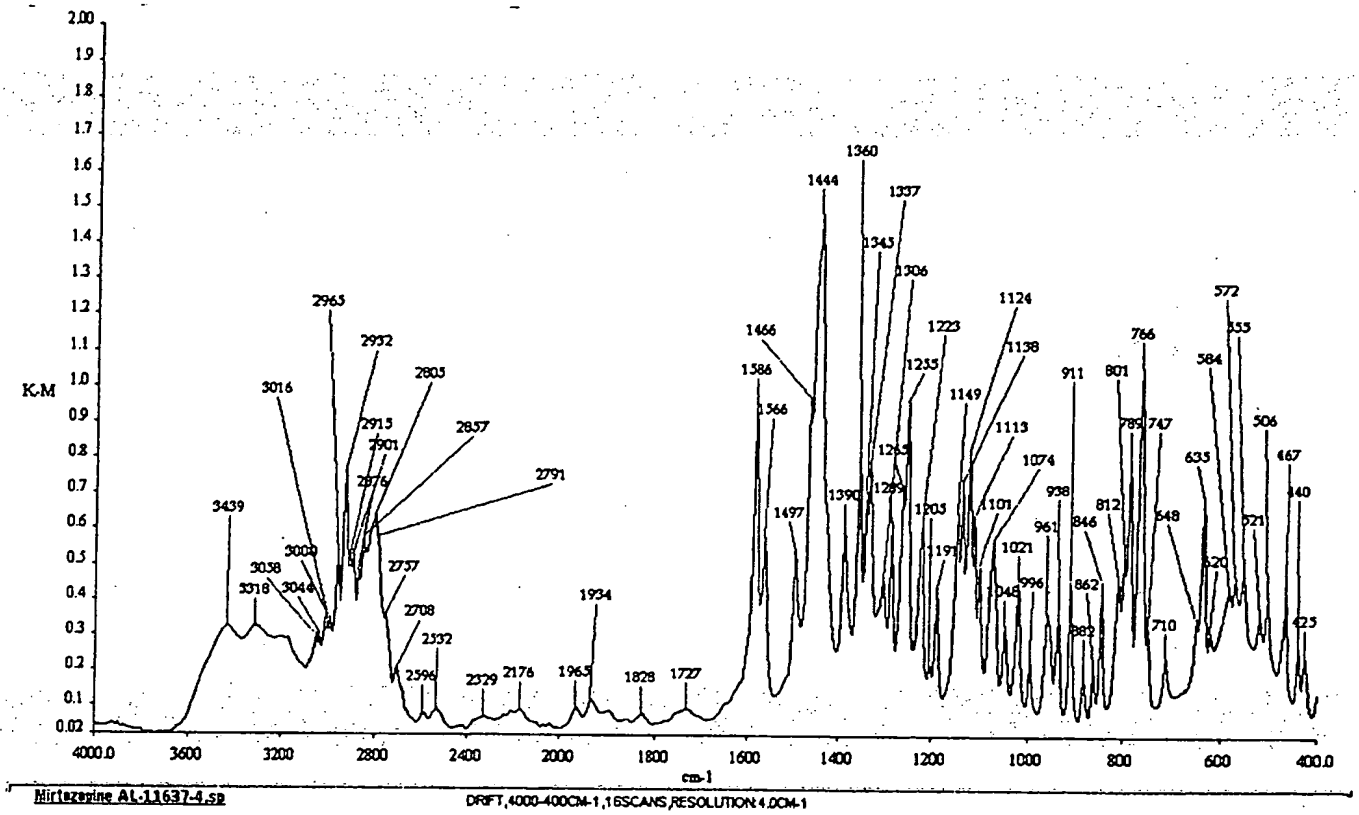
33.0
36.0
39.0
Deg.

Figure 1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3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
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3316
3038
3016
3000
2965
2932
2915
2901
2876
2857
2805
2791
2737
2708
2596
2332
2329
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1965
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1444
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1360
1343
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1306
1285
1265
1235
1223
1203
1191
1149
1138
1124
1113
1101
1074
1046
1021
996
961
938
911
862
846
812
801
789
766
747
710
635
584
572
553
548
521
506
467
440
425
Mirtazapine AL-11637-4.sp
DRIFT,4000-400CM-1,16SCANS,RESOLUTION 4.0CM-1

Figure 2

D4a

Mirtazapine was prepared in accordance with Example I.4 of US 4 062 848 (D4).

Reagents:

9.75 g	1-(3 hydroxymethylpyridyl-2)-2-phenyl-4-methyl-piperazine (hydroxy NMPP) CN = 422302803
19.5 ml	concentrated H_2SO_4

9.75 g of the hydroxy NMPP was added to a three necked flask equipped with a mechanical stirrer, thermometer and condenser. 19.5 ml of concentrated H_2SO_4 was added dropwise and with stirring at room temperature over 1 hour. During the addition the temperature rose to about 35 °C. The reaction mixture was stirred for 5 hours at 35 – 45 °C until a clean solution was obtained. 180.0 g ice and 66.0 ml NH_4OH (25 %) was added. An oily product was obtained.

250 ml of chloroform was added to the oily product and the mixture was stirred for 1 hour. Phases were separated and the aqueous layer was extracted with 2 x 100 ml chloroform. The combined chloroform extracts were dried over Na_2SO_4, filtered and concentrated to dryness to give 13.32 g oily product which was further stored for work up at room temperature (~ 22-25 °C).

70.0 ml of ether was added to the oily product and the mixture was stirred for 1 hour at room temperature. The ether was concentrated to 2 V and the precipitate was filtrated to give 7.0 g of solid crude. 75.7 v (530.0 ml) petroleum ether 40-60 was added to the crude solid (7.0 g) at reflux. This produced a turbid solution. The solution was stirred for 1-2 hours and no precipitate was observed.

The petroleum ether was concentrated to 3V. A precipitate was obtained. This was filtered and dried at 40 °C vacuum (10-15 mmHg) for 17 hours. 5.15 g of creamy powder was obtained.

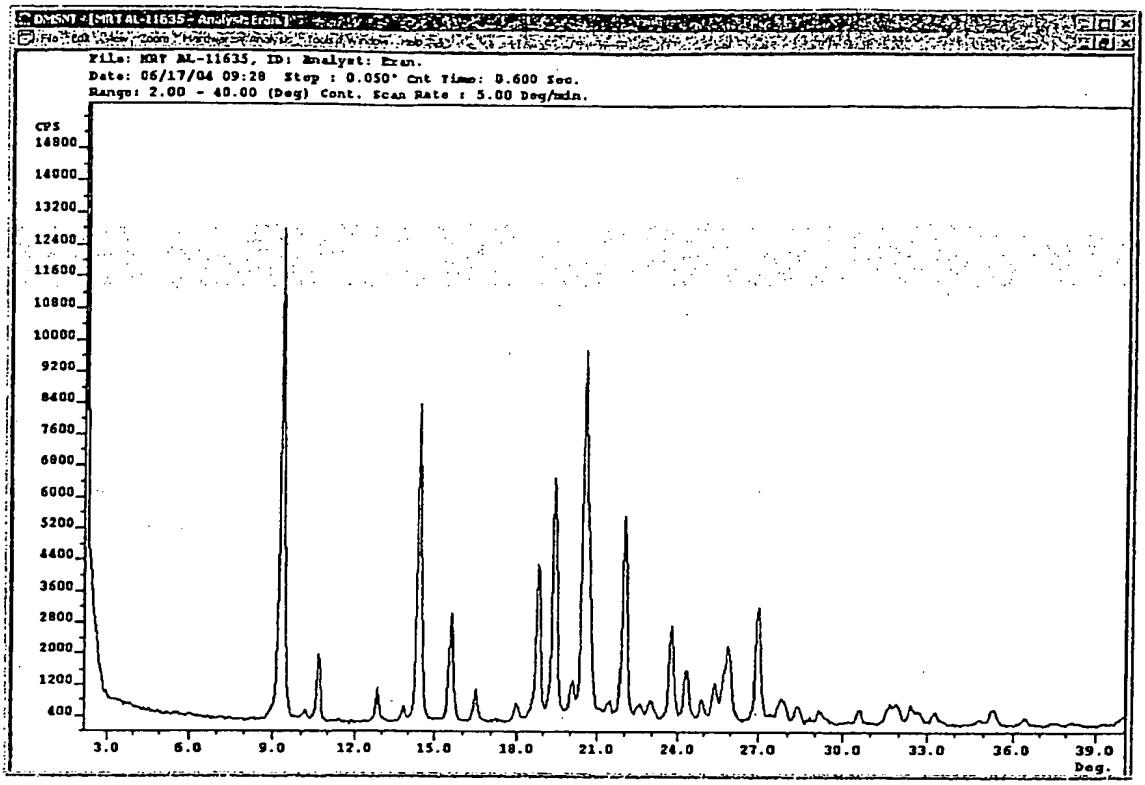
Table D4a contains results of analysis of the mirtazapine so-obtained.

Table D4a

Water content (wt %, Karl Fischer method)	2.8
Melting point (° C)	116.9
TLC (SiO_2)	MeOH-AcOH (9:1); R_f 0.47

Figure 3 is an X-ray diffraction spectrum of the mirtazapine.
Details of measurement are as for Figure 1

Figure 4 is an IR spectrum of the mirtazapine.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Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 5.00 Deg/min.
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3.0
6.0
9.0
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33.0
36.0
39.0
Deg.

Figure 3

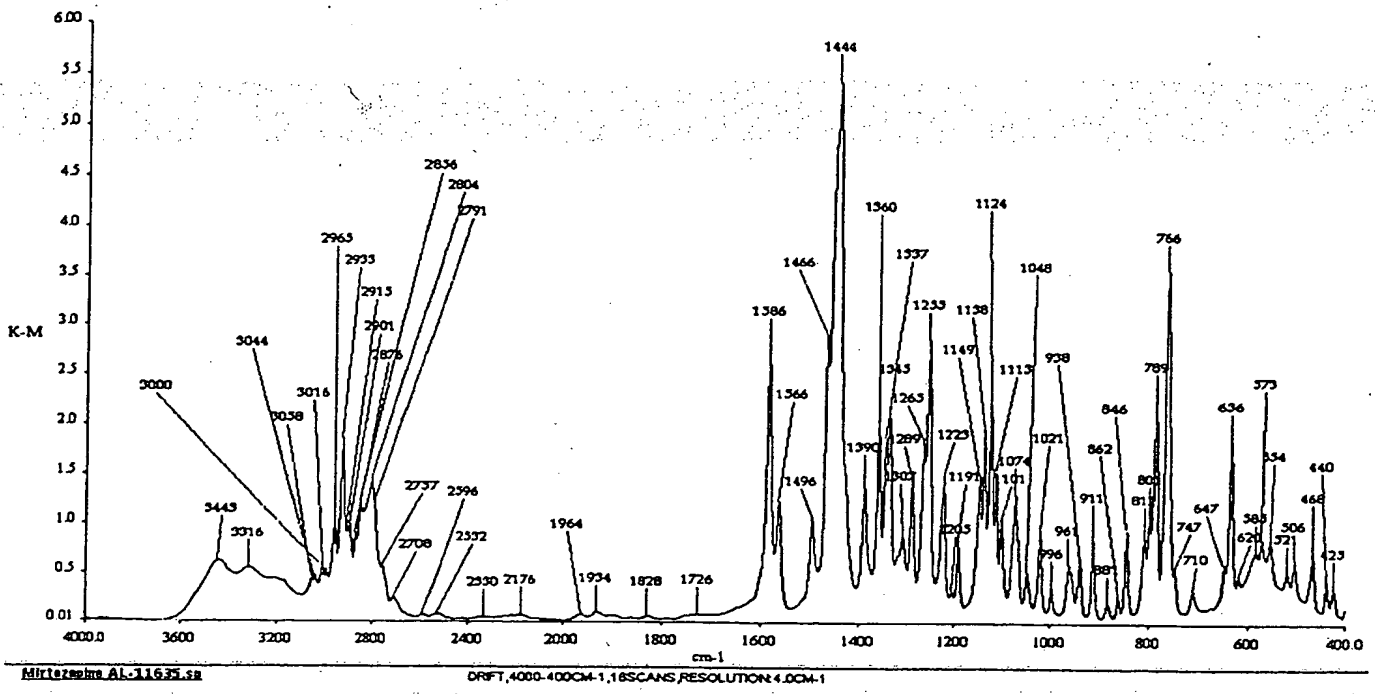
K-M
cm-1
Mirtazapine AL-11635.sa
DRIFT,4000-400CM-1,16SCANS,RESOLUTION 4.0CM-1

Figure 4